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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,301	09/10/2003	Brett P. Giroir	UTSD:1477	5400

23379 7590 06/26/2008

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ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/26/2008	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BRETT P. GIROIR, MONTE S. WILLIS,
and TIMOTHY S. CHURCH

Appeal 2007-4508
Application 10/660,301
Technology Center 1600

Decided: June 24, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-19. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1, 7, and 15 are the independent claims on appeal, and read as follows:

1. A method of determining cardiovascular risk in a person without cardiovascular disease or diagnosis thereof, the method comprising the steps of:

determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, and a further step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

7. A method for characterizing a risk of developing a future cardiovascular disorder in an apparently healthy individual, the method comprising steps:

obtaining a test MIF level in the blood, saliva or urine of the individual,

comparing the test MIF level to a predetermined control MIF value, and

characterizing the individual's risk of developing the future cardiovascular disorder based upon the test MIF level in comparison to the predetermined control MIF value.

15. A method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder, the method comprising steps:

obtaining a test MIF level in the blood, saliva or urine of the individual, and

comparing the test MIF level to a predetermined control MIF value,

wherein the test MIF level in comparison to the predetermined control MIF value is indicative of whether the individual will benefit from treatment with said agent.

We affirm-in-part.

BACKGROUND

According to the Specification,

> Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine/hormone that has been associated with a number of disease states. MIF expression has been suggested to correlate with diseases like sepsis, prostate cancer, aneurysmal expansion, acute myocardial infarction, atherosclerosis, diabetes, etc., and bypass surgery. . . .
>
> We have determined that the serum level of MIF is extremely elevated in patients with high cardiovascular risk, and that it falls rapidly when interventions are made which reduce this risk. Prior to our work, MIF levels have never been associated with cardiovascular risk in non-diseased or non-diagnosed persons. Like CRP, ME is a marker of cardiovascular risk providing clinically important prognostic information in the assessment of overall cardiovascular risk.

(Spec. 1-2 (references omitted).)

DISCUSSION

Indefiniteness

Claims 1-14 and 17[1] stand rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention." (Ans. 3)

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if

[1] The Examiner rejected claims 1-19 under 35 U.S.C. § 112, second paragraph, but none of the rejections apply to claims 15, 16, 18, and 19.

"the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1987).

The Examiner objects to the use of the phrase "cardiovascular risk metric" in claims 1-7, asserting that the "metes and bounds of the phrase is unclear and ambiguous." (Ans. 3.) According to the Examiner, "the [S]pecification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable [sic] apprised of the metes and bounds of the claimed 'cardiovascular risk metric.'" (*Id.*)

Appellants argue that the step of assigning a cardiovascular risk metric "requires no more than assigning to the person a metric proportional to his/her MIF concentration," and that the "particular form of the metric used is discretionary to the practitioner; e.g. numerical metrics such as 'risk level 1, risk level 2, etc.' or more descriptive metrics such as 'very high risk, high risk, normal risk, low risk, etc.'" (Reply Br. 2.)

We agree with Appellants that the use of the phrase "cardiovascular risk metric" as used in the step of "assigning a cardiovascular risk metric" would be understood by the skilled artisan. The Examiner may be concerned with the breadth of the phrase, but "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (CCPA 1971); *see also In re Hyatt*, 708 F.2d 712, 714-15 (Fed. Cir. 1983). We thus reverse the rejection as it applies to claims 1-7.

The Examiner also objects to the phrases "apparently healthy individual" (claim 7) and "the individual is apparently healthy" (claim 13) in

claims 7-14 and 17(Ans. 3). The Examiner notes that the Specification "discloses that the 'apparently healthy individual' and 'the individual is apparently healthy' can be statistically or professionally determined overweight or obese persons and/or subject to or predisposed to type II diabetes." (*Id.*) According to the Examiner, however, it "is not clear what constitutes 'apparently healthy individual' and 'the individual is apparently healthy' because obese persons or those subject to or predisposed to type II diabetes are not 'apparently healthy individual; and 'the individual is apparently healthy'; as such the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonable [sic] apprised of the metes and bounds of the claimed 'apparently healthy individual' and the 'individual is apparently healthy'." (*Id.* at 4.)

Appellants argue that a cardiovascular professional (one of ordinary skill in the art) "would understand the meets and bounds of this phrase," and that its use in the Specification and the claims "is consistent with how one skilled in the art would understand this term." (App. Br.[2] 5.)

Appellants also rely on the Declaration of Dr. Brett Paul Girour (one of the inventors) submitted under 37 C.F.R. § 1.132 to establish "that the claims are sufficiently clear such that one of ordinary skill in the art to which the invention pertains would understand the metes and bounds of the claims and be on notice as to what is the scope of the claims." (*Id.* at 5.) The Declaration reiterates Appellants arguments made in the Appeal Brief (Declaration ¶ 2).

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[2] All references to the Appeal Brief (App. Br.) are to the "Supplemental Brief on Appeal" dated April 30, 2007.

We agree with the Examiner that the metes and bounds of the phrases "apparently healthy individual" (claim 7) and "the individual is apparently healthy" (claim 13) is unclear. Moreover, in response, Appellants merely argue that the skilled artisan, *i.e.*, a cardiovascular professional, would understand the metes and bounds, without providing any explanation as to how that skilled artisan would interpret the objected to phrases.

Finally, the Examiner objects to the limitation in claims 11-14 of "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values." (Ans. 4.) According to the Examiner,

> "it is not clear what the claimed first risk value, the second risk value and the third risk value are and how these risk values relate to the disclosed known markers of heart disease; as such one skill [sic] in the art would not be reasonable [sic] apprised of the metes and bounds of these risk values, much less to characterize the individual's risk of developing the cardiovascular disorder based upon these risk values."

(*Id.* at 5.)

Appellants argue that what is meant by the objected to phrase "is evident to one skilled in the art in view of the Specification," and that one of "ordinary skill in the art . . . would understand the metes and bounds of this phrase." (App. Br. 5.)

Appellants again rely on the Declaration of Dr. Brett Paul Girour (one of the inventors) in confirming "that the claims are sufficiently clear such that one of ordinary skill in the art to which the invention pertains would understand the metes and bounds of the claims and be on notice as to what is

the scope of the claims." (*Id.* at 5.) The Declaration reiterates Appellants' arguments made in the Appeal Brief (Declaration ¶ 2).

We agree with the Examiner that the metes and bounds of the phrase "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third value different from said first and second risk values" is unclear. Moreover, we note again that in response, Appellants merely argue that the skilled artisan, *i.e.*, a cardiovascular professional, would understand the metes and bounds, without providing any explanation as to how that skilled artisan would interpret the phrase.

New Matter

Claims 1-19 stand rejected under 35 U.S.C. first paragraph, "as failing to comply with the written description requirement." (Ans. 8.) This is a new matter rejection.

The Examiner finds that "a *test* MIF concentration" and "a *control* MIF concentration" as found in claims 1-19 are not supported by the disclosure as filed (Ans. 8).

The disclosure as originally filed need not provide "*in haec verba* support for the claimed subject matter at issue," rather, the disclosure should convey to one skilled in the art that the inventor was had possession of the invention at the time of filing. *Purdue Pharma L.P. v. Faulding Pharmaceutical Co.,* 230 F.3d 1320, 1323 (Fed. Cir. 2000) (citations omitted).

Appellants argue that the "concept of a 'marker of cardiovascular risk' implies to one skilled in the art that the marker is different in the risk group and the corresponding control group," and that "what you call the compared-to measure ('control', 'predetermined value', etc) are arbitrary and self-evident, inherent measures required for a disease 'marker.'" (App. Br. 9, relying of Spec. p. 3, ll. 14-20; p4, ll. 11-16; and p. 5, claim 7.)

We agree, and the rejection is reversed as to the use of the phrases "a *test* MIF concentration" and "a *control* MIF concentration."

The Examiner also finds that the phrase "*not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk*" as required by claims 1-6 is not supported by the disclosure as filed (Ans. 8).

Appellants do not present any argument or point to any place in the disclosure as originally filed where support for the phrase may be found. We therefore summarily affirm the rejection. *See Hyatt v. Dudas*, 492 F.3d 1365, 1370 (Fed. Cir. 2007) ("In the context of the written description requirement, an adequate prima facie case must . . . sufficiently explain to the applicant what, in the examiner's view, is missing from the written description.") The rejection is thus affirmed as to claims 1-6.

Therefore, the rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph, as to new matter, is affirmed as to claims 1-6, but reversed as to claims 7-19.

Enablement

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

The Examiner notes that the Specification teaches that MIF is elevated in adults with high cardiovascular risk, and that serum MIF falls with reduction of cardiovascular risk (Ans. 5). The Examiner asserts, however, that it "is unpredictable whether MIF can be used as a marker for cardiovascular risk for any person *not predetermined to be subject to cardiovascular disease and/or apparently healthy individual* as broadly claimed." (*Id.* at 6.)

The Examiner cites Pan[3] for its disclosure that high serum MIF levels have been described in a variety of diseases such as rheumatoid arthritis, sepsis, asthma, and uvetis malarial anemia, glomerulonephritis, chronic colitis, and multiple sclerosis, thus demonstrating that MIF concentrations "would not necessarily be associated with cardiovascular risk." (Ans. 6.)

The Examiner argues further that the selection of appropriate controls and the interpretation of their results can be controversial (*id.*). Thus, the Examiner asserts, it is "unpredictable to decide what constitutes the claims *'a person not predetermined to be subject to cardiovascular disease' and/or an apparently healthy individual* to practice the claimed methods." (*Id.*)

The Examiner further cites Church,[4] which studied MIF levels in obese patients (Ans. 7). According to the Examiner, Church discloses that the elevation of MIF levels was not uniform across individuals, and it was not clear why some individuals had an elevated level while others did not, and factors such as weight, waist girth, C-reactive protein, or other cardiovascular disease risk factors were not associated with elevated MIF

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[3] Pan, "Macrophage migration inhibitory factor is associated with aneurismal expansion," *J. Vasc. Surg.*, Vol. 37, pp. 628-35 (2003).
[4] Church, "Obesity, macrophage migration inhibitory factor, and weight loss," *Int'l J. of Obesity*, Vol. 29, pp. 675-81 (2005).

levels (*id.*). The Examiner further relies on van Dielan[5] for its teaching that "MIF levels in morbidly obese individuals are low, and increase post gastric bypass surgery with decreasing body weight." (Ans. 7.) According to the Examiner, those results "*are clearly opposite to the disclosure of the instant specification in that the obese individuals have increased serum MIF level (see Examples on page*[*s*] *of the instant specification).*" (*Id.*)

The Examiner bears the initial burden of showing nonenablement. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). "[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' . . . That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (emphasis in original). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

In response, Appellants cite Garner,[6] which confirms "that MIF is a cardiac-derived myocardial depressant factor (Title)," and that Church, cited by the Examiner, notes that "MIF has been implicated as a causal

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[5] van Dielen, "Macrophage Inhibitory Factor, Plasminogen Activator Inhibitor-1, Other Acute Phase Proteins, and Inflammatory Mediators Normalize as a Result of Weight Loss in Morbidly Obese Subjects Treated with Gastric Restrictive Surgery," *J. Clin. Endocrinol. Metab.*, Vol. 89, pp. 4062-68 (2004).

[6] Garner, "Macrophage migration inhibitory factor is a cardiac-derived myocardial depressant factor," *Am. J. Heart Circ. Physiol.*, Vol. 285, pp. H2500-9 (2003).

mechanism in cardiovascular disease." (App. Br. 8.) Appellants argue further that the

> Examiner's criticisms that the elevated MIF concentrations Church found in obesity was not uniform across the examined individuals (e.g. Church et al., Abstract, lines l6-17), or that it may be difficult to difficult [sic] to idealize a control for certain extreme populations (e.g. Pan et al., 632, col 2, lines 27-29), or that a small group of morbidly obese had peculiar plasma MIF levels after gastric restrictive surgery (e.g. van Dielen et al., J Clin Endocrinol & Metabolism 89, 4062-65) are misplaced. Our invention relates to the identification of MIF as a marker for cardiovascular disease, and our claims are accordingly directed to a method of determining cardiovascular risk by identifying an elevated MIF level in a person, and (for example) assigning to the person a cardiovascular risk metric is [sic] accordance with the MIF level. Our claims to [sic] not require a perfect correlation between MIF and cardiovascular disease in every individual, or in every post-surgical context—there is no such thing for any marker. Our claims require only a populational association between elevated MIF and cardiovascular risk sufficient to use elevated MIF as a rational marker for such risk. Hence, whether or not MIF concentrations are uniformly elevated across a particular population of obese individuals, or whether or not MIF concentrations in that same obese populations correlated with CRP levels has no bearing on premise of our claims, that elevated MIF can be used as an indicator of cardiovascular risk.

(App. Br. 8-9.)

We conclude that Appellants have the better argument. Church, relied upon by the Examiner to demonstrate the unpredictability of the art, teaches that MIF plays a role in atherosclerotic plaque formation, and may play an important role in the development of cardiovascular disease (Church, p. 675). Garner, relied upon Appellants, also supports the role of MIF in cardiovascular disease, teaching that MIF functions as an important late

mediator of endotoxin-induced cardiac dysfunction in vivo (Garner, p. H2505). van Dielen, also relied upon by the Examiner to demonstrate the unpredictability of the art, looked at morbidly obese individuals, noting that such individuals have reduced insulin sensitivity, which may explain the decreased MIF levels, but insulin sensitivity increases as the individual loses weight, thus explaining increased MIF levels (van Dielen, pp. 4505-06). Thus, the references are not convincing on the issue of enablement, and the rejection to the extent it is based on the above rationale of the Examiner, is reversed.

> The Examiner further concludes in regard to claim 11 that
>
> the instant method encompasses "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk values [sic] different from said first and second risk values." However, the instant specification does not appear to disclose how the third risk values are established from the first and second risk value and what constitutes third risk values."

(Ans. 7)

As Appellants do not explain how the disclosure enables how the third risk values are established from the first and second risk value and what constitutes third risk value, the rejection as to claim 11, and the claims dependent thereon, *i.e.*, claims 12-14, is affirmed.[7]

[7] Arguments that Appellants could have made but chose not to make in the Briefs have not been considered and are deemed to be waived. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Thus, the rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement, is affirmed as to claims 11-14 but reversed as to claims 1-10 and 15-19.

Anticipation

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Yabunaka.[8]

Yabunaka is cited for teaching a comparison of serum MIF concentrations of type 2 diabetic patients to healthy control subjects (Ans. 9). The Examiner finds that Yabunaka assigns a cardiovascular risk metric as type II diabetes reads on a cardiovascular risk metric (*id.*).

It is axiomatic that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997).

Appellants argue that

> Yabanuka [ ] [sic] neither teach nor suggest the claimed two-step method. Yabanuka [ ] [sic] do not suggest that MIF is a marker for cardiovascular risk. To the contrary, they suggest it is not useful as any specific disease marker, but rather is a non-specific marker for illness in general. Since Yabanuka [sic] does not teach or suggest that MIF is a marker of cardiovascular risk, the reference can not anticipate our claims.
>
> Yabanuka [sic] does not assign to each subject person a cardiovascular risk metric in accordance with .their test MIF concentration. Nowhere does Yabanuka [sic] assign to any subject person anything *in accordance with his/her test MIF*

[8] Yabanuka, "Elevated Serum Content of Macrophage Migration Inhibitory Factor in Patients With Type 2 Diabetes," *Diabetes Care*, Vol. 23, pp. 256-258 (2000).

> *concentration.* Yabanuka's [sic] subjects are predetermined to have type 2 diabetes, and they are never assigned any measure of cardiovascular risk in accordance with their test MIF concentrations.

(App. Br. 11.)

The Examiner agrees that Yabunaka does not teach that MIF concentration is used as a specific marker for cardiovascular disease (Ans. 21), but asserts that "one of ordinary skill in the art could have combined the teachings of Yabanuka [ ] [sic]with his or her own knowledge to make the claimed method . . ." (Ans. 22).

That however, is an obviousness analysis, and does not constitute anticipation. We are thus compelled to reverse the rejection.

CONCLUSION

In summary:

As to the rejection of claims 1-19 rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention, we reverse as to claims 1-7 but affirm as to claims 10-14 and 17;

As to the rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph, for new matter, we affirm as to claims 1-6, but reverse as to claims 7-19;

As to the rejection of claims 1-19 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement, we affirm as to claims 11-14 but reverse as to claims 1-10 and 15-19.

As to the rejection claims 1 and 2 under 35 U.S.C. § 102(b) as being anticipated by Yabunaka, we reverse the rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a).

AFFIRMED-IN-PART

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